Comments on the Second External Review Draft of the "Integrated Science Assessment for Ozone and Related Photochemical Oxidants"

Prepared for the CASAC Ozone Panel

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Air Improvement Resource, Inc. (AIR) reviewed the second draft Integrated Science Assessment (ISA) for the Alliance of Automobile Manufacturers focusing on the portions of the document that are important to providing the Administrator with the relevant science with which to judge the health effects of ozone and establish a primary ozone standard which will protect the public health with an adequate margin of safety. AIR identified many issues with the draft ISA's evaluation of the data and provided detailed comments to the Agency.[1]

AIR comments focus on the background of ozone uncontrollable through reduction in US man-made emissions, the human clinical studies of ozone effects and their interpretation in terms of the public health, and the epidemiological studies of associations of ozone with health endpoints and their interpretation in terms of public health.

With regard to background ozone, there is substantial new information that the background is higher than EPA estimated in the previous review. The new higher background estimates affect consideration of both the primary and secondary standards. Dr. George Wolff of AIR will be presenting separate comments on the new information regarding background ozone.

Controlled Human Exposures

The controlled human exposure studies provide a strong body of information on the dose-response of effects of 1-to-3 hour and 6- to 8-hour exposures to ozone. The first effects - transient, reversible FEV1 decrements - are the body's reflexive reaction to the presence of an irritant gas unrelated to sensations of discomfort. Such effects occur after exposures to 0.08 ppm for 6 to 8 hours when the subjects are exercising at a rate that would be considered strenuous when carried out intermittently for an eight-hour period. There are now several studies of exposure to 0.060 ppm with exercise that all indicate

[1] J. M. Heuss, G. T. Wolff, and D. F. Kahlbaum, Review and Critique of the U. S. Environmental Protection Agency's Second External Review Draft of the Integrated Science Assessment for Ozone and Related Photochemical Oxidants, Air Improvement Resource, Inc. Report Prepared for The Alliance of Automobile Manufacturers, November 28, 2011. Docket No. EPA-HQ-ORD-0050-0023.

very small group mean changes in FEV1, changes of the same magnitude as the accuracy of repeat FEV1 measurements. Importantly, respiratory symptoms were not affected by ozone exposure at the 0.060 ppm level.

The public health significance of the first effects of ozone is not adequately discussed in the ISA. According to the American Thoracic Society guidelines, the functional changes at 0.06 ppm would not be considered as adverse. The knowledge of the basic nature and extent of functional effects has not changed substantially since the 1997 and 2008 reviews. The fact that the first effects on the performance of lung function tests occur at 0.50 ppm in sedentary individuals, together with the fact that personal exposures to ozone are only a fraction of the monitored levels provides a large margin of safety from the first effects identified in controlled human studies for the vast bulk of the population as they go about their daily activities.

The threshold nature of the clinical effects is acknowledged at several points in the text of the ISA, but the implications of this finding are not adequately considered in the integrative synthesis. For example, the Mudway and Kelly, 2004 meta-analysis of 21 studies of the presence of inflammatory markers showed that neutrophil influx in healthy subjects is associated with total ozone dose (i.e., the product of ozone concentration, exposure duration, and ventilation rate) with a threshold. Moreover, W, F. McDonnell's comments to CASAC[2] note that his dynamic exposure model for ozone-induced FEV1 decrements has now been modified to include a threshold.

In addition, the existence of a substantial threshold for the first physiological effects in controlled studies is not consistent with EPA's assumption that the more severe effects suggested by some epidemiological studies have no threshold. Such an assumption is not consistent with either the general principles of toxicology or the specific findings of ozone toxicological studies.

As noted in the AIR comments to the Agency, the results of the clinical studies cannot be used directly to claim effects below the current standard. Rather, they must be used to evaluate the risk by mapping the results onto realistic exposure/activity patterns. Although this is done in a separate Risk Assessment (RA), the science supporting the key data and assumptions that go into the Risk Assessment should be fully vetted in the ISA. The current draft ISA is deficient in this regard. For example, McDonnell asks that the ISA discuss the performance and benefits of his model as a basis for EPA updating its RA. The AIR comments to the Agency raised several additional issues. For example, the ISA should acknowledge that ozone at breathing height is lower than ozone at measurement height. This was acknowledged in the 2006 Criteria Document and the

[2] W. F. McDonnell, Comments Prepared for the CASAC Review of the Second External Review Draft Integrated Science Assessment for Ozone and Related Photochemical Oxidants, Research Triangle Park, NC, January 9-10, 2012, "Identification and Evaluation of a Dynamic Ozone-FEV1 Exposure-Response Model For Use in Conducting Risk Assessment in Support of the NAAQS for Ozone."

analogous difference between ozone at plant height and ozone at measurement height is already acknowledged in the draft ISA. Importantly, since exercise or ventilation rate is such an important factor in assessing risk for ozone effects, the ISA should include a discussion of the distribution of ventilation rates in the human population. The November 28, 2011 AIR comments documented that the APEX model EPA used in the previous RA predicts more elevated ventilation rate occurrences than observed in real world data.

Epidemiological Studies

The epidemiological or observational studies of the association of ozone with various health endpoints continue to be difficult to interpret. As more studies are published, the fundamental weaknesses of this body of information have become more apparent. For example, publication bias is now known to exaggerate the apparent strength and consistency of association. Limitations due to issues of model selection and stochastic variability add substantially to the uncertainty. In addition, the issue of confounding raises the possibility that a positive association for ozone or any other pollutant in a single-pollutant model may be an indicator of some other pollutant or factor rather than evidence of an independent effect of that pollutant. EPA's practice of making causality determinations for broad categories of effects is misleading because the evidence of causality for the various health endpoints in a given broad category varies widely.

The second draft ISA continues to over-rely on the positive ozone associations in the literature, discount evidence from studies that report null or negative results, and avoid a rigorous and balanced discussion of biological plausibility. As a result, the second draft continues to inappropriately weigh the evidence from epidemiology with regard to ozone and health.

While there is evidence of small acute FEV1 changes, the lack of consistent evidence implicating ozone as being associated with inflammation or respiratory symptoms in observational studies is an important finding that needs to be considered as the ISA evaluates the biological plausibility of even more severe effects such as daily hospital admissions and mortality.

With regard to hospital admissions and mortality, the overall results of a large multi-continent Health Effects Institute (HEI) study (APHENA) do not support EPA's claims of causal relationships between ozone and mortality or between ozone and hospital admissions. The ISA uses selected results from the HEI study and the literature in general to claim consistent or generally positive effects on mortality and hospital admissions. However, the full pattern of results for these endpoints demonstrates a wide range from positive to negative associations in individual cities in multi-city studies and a regional and seasonal pattern of combined associations that is not consistent with ozone causality. Details of these criticisms are provided in the November 28, 2011 AIR comments. We also note that HEI submitted comments that support AIR's point that the draft ISA draws stronger conclusions regarding the APHENA results than would the

investigators, the HEI Review Committee, or the data itself permit.[3] HEI indicates "This is especially true of the complex results from the analyses of respiratory vs. cardiovascular mortality and the not-strongly-coherent results of the mortality and hospitalization analyses."

The overall evidence for cardiovascular effects from current ambient ozone concentrations is weak and inconsistent. The ISA acknowledges the lack of a consistent cardiovascular morbidity signal and weak evidence for biological plausibility for ozone-induced cardiovascular morbidity. Therefore, the body of evidence is not suggestive of a causal relationship between relevant short-term exposures to O_3 and cardiovascular effects.

With regard to chronic mortality, the ISA focuses on one positive study, Jerrett et al. (2009), as showing a chronic respiratory mortality signal for ozone. However, the respiratory mortality signal is present only for females in spite of the fact that males would be expected to receive higher ozone doses by being outside exercising more than females. In addition, the regional results reported by Jerrett et al. show no respiratory mortality effect in Southern California, the Northeast, or the Industrial Midwest, the regions of the country with the highest historic man-made ozone exposures. Moreover there are several other chronic mortality studies that do not report an ozone effect. Finally, the presence of a chronic respiratory mortality signal is not coherent with the lack of an acute respiratory mortality signal in the HEI APHENA study. For these reasons, the evidence for a chronic ozone mortality effect is much weaker than indicated in the draft ISA.

[3] December 29, 2011 HEI letter from D. Greenbaum to Drs. Vandenberg and Samet, Docket No. EPA-HQ-ORD-0050-0028.